Selección de Resúmenes de Menopausia

Semana del 15 al 21 de Julio de 2015

Juan Enrique Blümel. Departamento Medicina Sur. Universidad de Chile

Atherosclerosis. 2015 Jul 2;242(1):87-96. doi: 10.1016/j.atherosclerosis.2015.06.056. [Epub ahead of print]

Tibolone decreases Lipoprotein(a) levels in postmenopausal women: A systematic review and meta-analysis of 12 studies with 1009 patients.

Kotani K, Sahebkar A, Serban C, Andrica F, Toth PP, Jones SR, Kostner K, Blaha MJ, Martin S, Rysz J, et al.

INTRODUCTION: Circulating lipoprotein (a) (Lp(a)) is a recognized risk factor for cardiovascular disease (CVD). Tibolone, a synthetic steroid, may lower Lp(a) levels; however, evidence of the effects of tibolone on Lp(a) still remain to be defined. Therefore, we investigated the effects of tibolone treatment on circulating Lp(a) levels in postmenopausal women. METHODS: The search included PUBMED, Web of Science, Scopus, and Google Scholar (up to January 31st, 2015) to identify controlled clinical studies investigating the effects of oral tibolone treatment on Lp(a) levels in postmenopausal women. Random-effects meta-regression was performed using unrestricted maximum likelihood method for the association between calculated weighted mean difference (WMD) and potential moderators. RESULTS: Meta-analysis of data from 12 trials (16 treatment arms) suggested a significant reduction of Lp(a) levels following tibolone treatment (WMD: -25.28%, 95% confidence interval [CI]: -36.50, -14.06; $p < 0.001$). This result was robust in the sensitivity analysis and its significance was not influenced after omitting each of the included studies from the meta-analysis. When the studies were categorized according to the tibolone dose, there were consistent significant reductions of Lp(a) in the subsets of studies with doses <2.5 mg/day (WMD: -17.00%, 95%CI: -30.22, -3.77; $p < 0.012$) and 2.5 mg/day (WMD: -29.18%, 95%CI: -45.02, -13.33; $p < 0.001$). Likewise, there were similar reductions in the subsets of trials with follow-up either <24 months (WMD: -26.79%, 95%CI: -38.40, -15.17; $p < 0.001$) or ≥24 months (WMD: -23.10%, 95%CI: -40.17, -6.03; $p = 0.008$). CONCLUSIONS: This meta-analysis shows that oral tibolone treatment significantly lowers circulating Lp(a) levels in postmenopausal women. Further studies are warranted to explore the mechanism of this effect and the potential value and place of tibolone or its analogues in the treatment of elevated Lp(a) in individuals at risk of CVD.

J Natl Cancer Inst. 2015 Jul 16;107(9). pii: djv169. Print 2015 Sep.

Circulating Adipokines and Inflammatory Markers and Postmenopausal Breast Cancer Risk.

Gunter MJ, Wang T, Cushman M, Xue X, Wassertheil-Smoller S, Strickler HD, Rohan TE, Manson JE, et al.

BACKGROUND: Adipokines and inflammation may provide a mechanistic link between obesity and postmenopausal breast cancer, yet epidemiologic data on their associations with breast cancer risk are limited. METHODS: In a case-cohort analysis nested within the Women's Health Initiative Observational Study, a prospective cohort ofpostmenopausal women, baseline plasma samples from 875 incident breast cancer case patients and 839 subcohort participants were tested for levels of seven adipokines, namely leptin, adiponectin, resistin, interleukin-6, tumor necrosis factor-α, hepatocyte growth factor, and plasminogen activator inhibitor-1, and for C-reactive protein (CRP), an inflammatory marker. Data were analyzed by multivariable Cox modeling that included established breast cancer risk factors and previously measured estradiol and insulin levels. All statistical tests were two-sided. RESULTS: The association between plasma CRP levels and breast cancer risk was dependent on hormone therapy (HT) use at baseline ($P_{interaction} = .003$). In a model that controlled for multiple breast cancer risk factors including body mass index (BMI), estradiol, and insulin, CRP level was positively associated with breast cancer risk among HT nonusers (hazard ratio for high vs low CRP levels = 1.67, 95% confidence interval = 1.04 to 2.68, $P_{trend} = .029$). None of the other adipokines were statistically significantly associated with breast cancer risk. Following inclusion of CRP, insulin, and estradiol in a multivariable model, the association of BMI with breast cancer was attenuated by 115%. CONCLUSION: These data indicate that CRP is a risk factor for postmenopausal breast cancer among HT nonusers. Inflammatory mediators, together with insulin and estrogen, may play a role in the obesity-breast cancer relation.

JAMA Oncol. 2015 Jun 11. doi: 10.1001/jamaoncol.2015.1546. [Epub ahead of print]

Overweight, Obesity, and Postmenopausal Invasive Breast Cancer Risk: A Secondary Analysis of the Women's Health Initiative Randomized Clinical Trials.

Neuhouser ML, Aragaki AK, Prentice RL, Manson JE, Chlebowski R, Carty CL, Ochs-Balcom HM, et al.

IMPORTANCE: More than two-thirds of US women are overweight or obese, placing them at increased risk for postmenopausal breast cancer. OBJECTIVE: To investigate in this secondary analysis the associations of overweight and obesity with risk of postmenopausal invasive breast cancer after extended follow-up in the Women's Health Initiative (WHI) clinical trials. DESIGN, SETTING, AND PARTICIPANTS: The WHI clinical trial protocol incorporated measured height and weight, baseline and annual or biennial mammography, and adjudicated breast cancer end points in 67 142 postmenopausal women ages 50 to 79 years at 40 US clinical centers. The women were enrolled from 1993 to 1998 with a median of 13 years of follow-up through 2010; 3388 invasive breast cancers were observed. MAIN OUTCOMES AND MEASURES: Height and weight were measured at baseline, and weight was measured annually thereafter. Data were collected on demographic characteristics, personal and family medical history, and personal habits (smoking, physical activity). Women underwent annual or biennial mammograms. Breast cancers were verified by medical records reviewed by physician adjudicators. RESULTS: Women who were overweight and obese had an increased invasive breast cancer risk vs women of normal weight. Risk was greatest for obesity grade 2 plus 3 (body mass index [BMI], calculated as weight in kilograms divided by height in meters squared, >35.0) (hazard ratio [HR] for invasive breast cancer, 1.58; 95% CI, 1.40-1.79). A BMI of 35.0 or higher was strongly associated with risk for estrogen receptor-positive and progesterone receptor-positive breast cancers (HR, 1.86; 95% CI, 1.60-2.17) but was not associated with estrogen receptor-negative cancers. Obesity grade 2 plus 3 was also associated with advanced disease, including larger tumor size (HR, 2.12; 95% CI, 1.67-2.69; P = .02), positive lymph nodes (HR, 1.89; 95% CI, 1.46-2.45; P = .06), regional and/or distant stage (HR, 1.94; 95% CI, 1.52-2.47; P = .05), and deaths after breast cancer (HR, 2.11; 95% CI, 1.57-2.84; P < .001). Women with a baseline BMI of less than 25.0 who gained more than 5% of body weight over the follow-up period had an increased breast cancer risk (HR, 1.36; 95% CI, 1.1-1.65), but among women already overweight or obese we found no association of weight change (gain or loss) with breast cancer during follow-up. There was no effect modification of the BMI-breast cancer relationship by postmenopausal hormone therapy, and the direction of association across BMI categories was similar for never, past, and current hormone therapy use. CONCLUSIONS AND RELEVANCE: Obesity is associated with increased invasive breast cancer risk in postmenopausal women. These clinically meaningful findings should motivate programs for obesity prevention.

JAMA Oncol. 2015 Jun 1;1(3):296-305. doi: 10.1001/jamaoncol.2015.0494.

Breast Cancer After Use of Estrogen Plus Progestin and Estrogen Alone: Analyses of Data From 2 Women's Health Initiative Randomized Clinical Trials.

Chlebowski RT, Rohan TE, Manson JE, Aragaki AK, Kaunitz A, Stefanick ML, Simon MS, et al.

IMPORTANCE: The use of menopausal hormone therapy (HT) continues in clinical practice, but reports are conflicting concerning the longer-term breast cancer effects of relatively short-term use. OBJECTIVE: To report the longer-term influence of menopausal HT on breast cancer incidence in the 2 Women's Health Initiative (WHI) randomized clinical trials. DESIGN, SETTING, AND PARTICIPANTS: A total of 27 347 postmenopausal women aged 50 to 79 years were enrolled at 40 US centers from 1993 to 1998 and followed up for a median of 13 years through September 2010. INTERVENTIONS: A total of 16 608 women with a uterus were randomized to conjugated equine estrogens (0.625 mg/d [estrogen]) plus medroxyprogesterone acetate (2.5 mg/d [progestin]) (E + P) or placebo with a median intervention duration of 5.6 years, and 10 739 women with prior hysterectomy were randomized to conjugated equine estrogens alone (0.625 mg/d) or placebo with a median intervention duration of 7.2 years. MAIN OUTCOMES AND MEASURES: Time-specific invasive breast cancer incidence rates and exploratory analyses of breast cancer characteristics by intervention and postintervention phases in the 2 HT trials. RESULTS: In the E + P trial, hazard ratios (HRs) for the influence of combined HT on breast cancer were lower than 1 for 2 years (HR, 0.71; 95% CI, 0.47-1.08) and steadily increased throughout intervention, becoming significantly increased for the entire intervention phase (HR, 1.24; 95% CI, 1.01-1.53). In the early

postintervention phase (within 2.75 years from intervention), there was a sharp decrease in breast cancer incidence in the combined HT group, though the HR remained higher than 1 (HR, 1.23; 95% CI, 0.90-1.70). During the late postintervention phase (requiring patient re-consent), the HR for breast cancer risk remained higher than 1 through 5.5 years (median) of additional follow-up (HR, 1.37; 95% CI, 1.06-1.77). In the estrogen alone trial, the HR for invasive breast cancer risk was lower than 1 throughout the intervention phase (HR, 0.79; 95% CI, 0.61-1.02) and remained lower than 1 in the early postintervention phase (HR, 0.55; 95% CI, 0.34-0.89), but risk reduction was not observed during the late postintervention follow-up (HR, 1.17; 95% CI, 0.73-1.87). Characteristics of breast cancers diagnosed during early and late postintervention phases differed in both trials. CONCLUSIONS AND RELEVANCE: In the E + P trial, the higher breast cancer risk seen during intervention was followed by a substantial drop in risk in the early postintervention phase, but a higher breast cancer risk remained during the late postintervention follow-up. In the estrogen alone trial, the lower breast cancer risk seen during intervention was sustained in the early postintervention phase but was not evident during the late postintervention follow-up.

Am J Clin Nutr. 2015 Jul 15. pii: ajcn109116. [Epub ahead of print]

Diets with high-fat cheese, high-fat meat, or carbohydrate on cardiovascular risk markers in overweight postmenopausal women: a randomized crossover trial.

Thorning TK, Raziani F, Bendsen NT, Astrup A, Tholstrup T, Raben A.

BACKGROUND: Heart associations recommend limited intake of saturated fat. However, effects of saturated fat on low-density lipoprotein (LDL)-cholesterol concentrations and cardiovascular disease risk might depend on nutrients and specific saturated fatty acids (SFAs) in food. OBJECTIVE: We explored the effects of cheese and meat as sources of SFAs or isocaloric replacement with carbohydrates on blood lipids, lipoproteins, and fecal excretion of fat and bile acids. DESIGN: The study was a randomized, crossover, open-label intervention in 14 overweight postmenopausal women. Three full-diet periods of 2-wk duration were provided separated by 2-wk washout periods. The isocaloric diets were as follows: 1) a high-cheese (96-120-g) intervention [i.e., intervention containing cheese (CHEESE)], 2) a macronutrient-matched nondairy, high-meat control [i.e., nondairy control with a high content of high-fat processed and unprocessed meat in amounts matching the saturated fat content from cheese in the intervention containing cheese (MEAT)], and 3) a nondairy, low-fat, high-carbohydrate control (i.e., nondairy low-fat control in which the energy from cheese fat and protein was isocalorically replaced by carbohydrates and lean meat (CARB). RESULTS: The CHEESE diet caused a 5% higher high-density lipoprotein (HDL)-cholesterol concentration ($P = 0.012$), an 8% higher apo A-I concentration ($P < 0.001$), and a 5% lower apoB:apo A-I ratio ($P = 0.008$) than with the CARB diet. Also, the MEAT diet caused an 8% higher HDL-cholesterol concentration ($P < 0.001$) and a 4% higher apo A-I concentration ($P = 0.033$) than with the CARB diet. Total cholesterol, LDL cholesterol, apoB, and triacylglycerol were similar with the 3 diets. Fecal fat excretion was 1.8 and 0.9 g higher with the CHEESE diet than with CARB and MEAT diets ($P < 0.001$ and $P = 0.004$, respectively) and 0.9 g higher with the MEAT diet than with the CARB diet ($P = 0.005$). CHEESE and MEAT diets caused higher fecal bile acid excretion than did the CARB diet ($P < 0.05$ and $P = 0.006$, respectively). The dominant type of bile acids excreted differed between CHEESE and MEAT diets. CONCLUSIONS: Diets with cheese and meat as primary sources of SFAs cause higher HDL cholesterol and apo A-I and, therefore, appear to be less atherogenic than is a low-fat, high-carbohydrate diet. Also, our findings confirm that cheese increases fecal fat excretion

J Clin Endocrinol Metab. 2015 Jul 15:JC20152110. [Epub ahead of print]

Cardiovascular Fat, Menopause and Sex Hormones in Women: The SWAN Cardiovascular Fat Ancillary Study.

El Khoudary SR, Shields KJ, Janssen I, Hanely C, Budoff M, Barinas-Mitchell E, Everson-Rose SA, et al.

CONTEXT: Cardiovascular risk increases in women after menopause. Mounting evidence demonstrates a role of cardiovascular fat (CF) in the pathogenesis of coronary heart disease (CHD), but no research has examined CF in relation to sex hormones or menopausal status in women. OBJECTIVE: To determine the relationship between CF depots, menopausal status, and endogenous sex hormones. DESIGN: Cross-sectional and longitudinal study designs. SETTING: The Study of Women's Health Across the Nation (SWAN) Heart. PARTICIPANTS: 456 women (mean age: 50.75 years); 62% pre-/early peri-, and 38% late peri-/postmenopausal. INTERVENTION:

Menopausal status, endogenous sex hormones measured simultaneously with CF volumes, and circulating estradiol available 4.80 years (median) prior to CF measures. MAIN OUTCOME MEASURES: Volumes of CF (epicardial (EAT), paracardial (PAT), total heart (TAT=EAT+PAT) and aortic perivascular adipose tissues (PVAT)) Results: In final models, late peri-/postmenopausal women had 9.88% more EAT, 20.72% more PAT, and 11.69% more TAT volumes than pre-/early peri-menopausal women, P <0.05. PVAT was not associated with menopausal status. In final models, lower estradiol concentrations were associated with greater volumes of PAT and TAT, P<0.05. Women with the greatest reduction in estradiol since baseline had greater volumes of PAT compared to women with the least reduction, P =0.02. CONCLUSIONS: Late peri-/postmenopausal women have greater volumes of heart fat compared with pre-/early peri-menopausal women independent of age, obesity and other covariates. Endogenous sex hormones are associated with CF. Perhaps CF plays a role in the higher risk of CHD reported in women after menopause.

J Intern Med. 2015 Jul 14. doi: 10.1111/joim.12394. [Epub ahead of print]

Calcium supplements: benefits and risks.

Reid IR, Bristow SM, Bolland MJ.

Calcium is an essential element in the diet, but there is continuing controversy regarding its optimal intake, and its role in the pathogenesis of osteoporosis. Most studies show little evidence of a relationship between calcium intake and bone density, or the rate of bone loss. Re-analysis of data from the placebo group from the Auckland Calcium Study demonstrates no relationship between dietary calcium intake and rate of bone loss over 5 years in healthy older women with intakes varying from <400 to >1500 mg day^{-1} . Thus, supplements are not needed within this range of intakes to compensate for a demonstrable dietary deficiency, but might be acting as weak anti-resorptive agents via effects on parathyroid hormone and calcitonin. Consistent with this, supplements do acutely reduce bone resorption and produce small short-term effects on bone density, without evidence of a cumulative density benefit. As a result, anti-fracture efficacy remains unproven, with no evidence to support hip fracture prevention (other than in a cohort with severe vitamin D deficiency) and total fracture numbers are reduced by 0-10%, depending on which meta-analysis is considered. Five recent large studies have failed to demonstrate fracture prevention in their primary analyses. This must be balanced against an increase in gastrointestinal side effects (including a doubling of hospital admissions for these problems), a 17% increase in renal calculi and a 20-40% increase in risk of myocardial infarction. Each of these adverse events alone neutralizes any possible benefit in fracture prevention. Thus, calcium supplements appear to have a negative risk-benefit effect, and so should not be used routinely in the prevention or treatment of osteoporosis.

Geburtshilfe Frauenheilkd. 2015 Jun;75(6):588-596.

Hormone Therapy and its Effect on the Prognosis in Breast Cancer Patients.

Rauh C, Schuetz F, Rack B, Stickeler E, Klar M, Orlowska-Volk M, Windfuhr-Blum M, Heil J Rom J, et al.

Introduction: Use of hormone therapy (HT) has declined dramatically in recent years. Some studies have reported that HT use before a diagnosis of breast cancer (BC) may be a prognostic factor in postmenopausal patients. This study aimed to examine the prognostic relevance of HT use before BC diagnosis. Methods: Four BC cohort studies in Germany were pooled, and 4492 postmenopausal patients with HT use data were identified. Patient data and tumor characteristics were compared between users and nonusers, along with overall survival (OS), distant metastasis-free survival (DMFS), and local recurrence-free survival (LRFS). Cox proportional hazards models were stratified by study center and adjusted for age at diagnosis, tumor stage, grading, nodal status, and hormone receptors. Results: Women with HT use before the diagnosis of BC were more likely to have a lower tumor stage, to be estrogen receptor-negative, and to have a lower grading. With regard to prognosis there were effects seen for OS, DMFS and LRFS, specifically in the subgroup of women with a positive hormone receptor. In these subgroups, BC patients had a better prognosis with previous HT use. Conclusions: HT use before a diagnosis of BC is associated with a more favorable prognosis in women with a positive hormone receptor status. It may be recommended that the prognostic factor HT should be documented and analyzed as a confounder for prognosis in studies of postmenopausal hormone-responsive breast cancers.